6. Referral procedures

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Community Procedures, Patient Health Protection
What is a Referral?

Procedure used to resolve issues over concerns on

QUALITY
EFFICACY
SAFETY
BENEFIT/RISK

...of a medicine or class of medicines
What is a Referral?

Medicine(s) is **REFERRED** to the Agency’s committees **CHMP** **PRAC**

...to make a recommendation for a common approach across the European Union

Information on referrals:


Types of safety referrals

Directive 2001/83/EC

• Article 31 “Union Interest”
• Article 107 i “Urgent Union Procedure”

Regulation EC No 726/2004

• Article 20
• Article 5(3) “Scientific Opinion”
Safety Referrals
New Pharmacovigilance legislation

The main pillars of change:

• Systematic involvement of PRAC
• Increased transparency
• Public involvement
• Character of urgency reinforced
Article 107i
Urgent Union Procedure

In which cases?

As a result of the evaluation of data resulting from PhV activities + **urgent** action is needed:

- **consideration of**
  - suspension/revocation of a product(s),
  - prohibition of supply,
  - non renewal of the license of a product;
  - new contra indication for its use,
  - reduction in the dose,
  - restriction to the indications.

- **based on safety concerns, from MAH**
  - interruption of placing on the market,
  - product withdrawn;

*New Safety Urgent issue identified with a medicine with urgent action needed in view of public health protection*
Urgent Union Procedure

• **Who can start?**
  
  Member States of the Union or the European Commission
  *(justification of the action(s) proposed/taken)*

• **How?**
  
  Notification circulated to the Agency, (other) Member States and European Commission

• **Which products?**
  
  *ALL medicines affected by urgent safety issue*
  
  *(e.g. a class of products, just one product approved in more than one MS and regardless of route of authorisation – nationally or centrally authorised)*

  Products involved are identified by each Member State
Urgent Union Procedure

**Keys points**

- PRAC performs the assessment following:
  - Collection of data;
- Very short timeframe (max. of 60 days);
- Public hearing may be held;
- SAG and ad-hoc expert meeting may be held;
- PRAC issues a recommendation;
- Temporary measures can be taken at any time;

*Announced on the Agency’s website*
Urgent Union Procedure

Collection of data

ANYONE CAN SUBMIT DATA
to be considered to the assessment

DEDICATED MAILBOX

TEMPLATE SUBMISSION FORM

Data submitted will be part of the assessment that will be publicly available
Urgent Union Procedure

Announcement

- Summary of the Safety issue and Action proposed
- Notification + scientific background
- Draft list of all products concerned
- Questions + timetable for assessment
- Information on Public hearing
- Submission of data (dedicated mailbox and template form)

Example: Diclofenac-containing medicinal product
- Consideration of the matter;
- Temporary measures needed?
- SAG/Ad-hoc expert meeting
- Public Hearing?
- Which data to ask?
- When & how to submit?

- Public Hearing?
- Temporary measures;
- SAG/Ad-hoc expert meeting
- Preliminary discussion;

- Public hearings held?
- Non-Public hearing
- Discussion

PRAC RECOMMENDATION
Urgent Union Procedure

PRAC recommendation

A. PRAC outcomes defined
   - no further evaluation or action is required at union level;
   - the MAH should conduct further evaluation of data together with the follow-up of the results of that evaluation;
   - the MAH should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
   - the MS or MAH should implement risk minimisation measures;
   - the MA should be suspended, revoked or not renewed;
   - the MA should be varied

B. TT for implementation (if NAPs/MRP/DCP)

C. PRAC divergent position(s)
Urgent Union Procedure

**PRAC recommendation**

**Publication**

**PRAC highlights**
- *Friday* of the PRAC plenary
- Press release (if applicable);
- Question & Answers-type document in lay language
Urgent Union Procedure

Overall process of decision

- **PRAC Recommendation**
  - Following week
  - No CAPs
  - At least one CAP

- **CMDh**
  - Immediate Position or within 30 days
  - Agreement by consensus

- **CHMP**
  - Immediate Opinion or within 30 days
  - Position by majority
  - Adoption of Opinion (maintenance, variation, suspension, revocation, refusal of renewal)

- **European Commission**
  - Timetable for MS Implementation
  - Commission Decision

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Urgent Union Procedure

**CHMP Opinion, CMDh position/agreement**

Publication

**CHMP/CMDh highlights**

- *Friday* of the monthly plenary
- CHMP Opinion + CHMP AR
- CMDh position/agreement
- Press release (if applicable)
- Question & Answers-type document in lay language
Article 31
Quality, safety or efficacy issues

• When?

✓ shall be applicable where the interests of the Union are involved;
✓ following concerns relating to the quality, safety or efficacy;
✓ a medicine or a class of medicines;
✓ No urgent action required (possible clock stop);
✓ urgent action to protect public health possible.

• Safety Art.31 vs. Q&E driven Art.31

✓ involvement of different Committees;
✓ pathways of announcement;
✓ Possibility of a Public hearing.
PHARMACOVIGILANCE CONCERNS

NAP/MRP/DCP → ARTICLE 31 PROCEDURE

- **Initiated by**
  - MS/EC/MAH

- **Time Limit**
  - 60 + 60 + 30 days (Possible clock stop)

- **Consultation**
  - MAHs (Written +/- oral)

- **Outcome**
  - Public hearing

  - PRAC recommendation

  - CHMP opinion or CMDh agreement/position

  - Commission decision if applicable

  - No specific provisions but MSs can suspend any time

**Urgent Action to protect public health**

**RE-EXAMINATION**
EFFICACY, QUALITY CONCERNS

NAP/MRP/DCP \rightarrow \text{ARTICLE 31 PROCEDURE}

- **Initiated by**: MS/EC/MAH
- **Time Limit**: 60 + 90 days (Possible clock stop)
- **Consultation**: MAHs
  - Written +/- oral
- **Outcome**: CHMP opinion
  - Commission Decision
    - Final (measures)
- **Urgent Action to protect public health**: No specific provisions but MSs can suspend any time during procedure

RE-EXAMINATION
In summary: **NO** urgent action required  (1/2)
Timelines:

PhV data

PRAC

CHMP

CMDh

Quality, Efficacy

Opinion Position Opinion

Re-examination possible

Timetable (150 active days)

Public Hearing?
Article 20
Quality, efficacy or safety issues

- Manufacturing and qualities issues?
  - Art.20 of the Reg. (EC) 726/2004 remains (Manufacturer/importer established within the Community territory no longer fulfilling the obligations laid down in Title IV of Directive 2001/83/EC)
  - For CAPs
  - Triggering body: EC or MS
  - To ensure public health:
    - provisional measures tool
    - possibility of MS to suspend the use of the product
  - No re-examination foreseen
Article 20 - safety issues

• *When pharmacovigilance data* are concerned
  ✓ involvement of different Committee
  ✓ pathways of announcement
  ✓ possibility of public hearing

CAPs, Or CAPs and NAPs?
Centrally (CAPs) + Nationally (NAPs) authorised products

<table>
<thead>
<tr>
<th>Article 20(8)</th>
<th>Art 20(9)</th>
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<tbody>
<tr>
<td><strong>only CAP(s)</strong></td>
<td><strong>CAP(s)+NAP(s)</strong></td>
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<tr>
<td>Procedural steps followed:</td>
<td>Procedure followed:</td>
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<td>the ones defined under the article 31 or 107i (depending upon the urgency of the PV matter)</td>
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<tr>
<td>Urgency?</td>
<td>Urgency?</td>
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<tr>
<td>YES</td>
<td>YES</td>
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<td>Art.20</td>
<td>Art.107i</td>
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<td>Steps of Art.107i</td>
<td>Art.31</td>
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## CAPs only: procedural steps (art. 107i vs. art. 31)

<table>
<thead>
<tr>
<th>Procedural steps defined under the art. 107i (urgent action needed), including:</th>
<th>Procedural steps defined under the art. 31 (non urgent action needed), including:</th>
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<tbody>
<tr>
<td>PRAC involvement</td>
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<td>Announce start of procedure in the web portal</td>
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<td><strong>Possibility for healthcare professionals and public to submit to the Agency relevant information to the procedure</strong></td>
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<td>Possibility for public hearing, non public hearing and oral explanation</td>
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<td><strong>60 days for PRAC recommendation following submission of the information</strong></td>
<td><strong>Timelines</strong> to be followed are the ones established in Article 32 of Directive 2001/83/EC</td>
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<td>Issue of a PRAC recommendation</td>
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<td><strong>Adoption of temporary measures at any stage of the procedure</strong></td>
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<tr>
<td>CHMP to adopt an Opinion within 30 days of the receipt of the PRAC recommendation</td>
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Safety Referrals
Some numbers

Referral procedures started in 2011
- Safety referrals: 36 (47%)
- Other articles: 41 (53%)

Referral procedures started in 2012
- Safety referrals: 19 (46%)
- Other articles: 22 (54%)
Safety Overview Pre PRAC

- **ART 20**
  - Gilenya
  - Rasilez
  - Avandia

- **ART 20 / 31**
  - MMR vaccines
  - Fibrin sealants (fibrinogen)
  - Biphosphonates
  - Somatropins

- **ART 5 (3)**
  - Pandemic vaccines
  - Angiotensin II receptors antagonists
Safety Overview Pre PRAC

Ergot derivates
  Terpenic derivatives
Nicardipine (B/R)
Nimesulide

Buflomedil
Meprobamate
Sibutramine
## Safety Overview – post PRAC

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<th>ART 31</th>
<th>PRAC</th>
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- Codeine
- Diclofenac
- Short Acting Beta Antagonists
- Hydroxyethyl Starch
- Almitrine
- Diacerein
Thank you

Any question?